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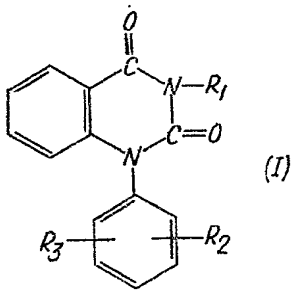
(54) QUINAZOLINEDIONE DERIVATIVES

(71) We, HISAMITSU PHARMACEUTICAL COMPANY, INC., a Japanese company of 408, Tashiro, Tosu City, Saga Prefecture, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to novel quinazolinedione derivatives and process for the production of the same, and, more particularly, to quinazolinedione derivatives and process for the production thereof expressed in the following general formula:



(I)

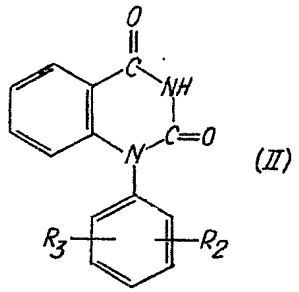
wherein R_1 represents an alkyl, a substituted alkyl or an acyl radical; R_2 and R_3 each represent a hydrogen atom, a CF_3 group, a Cl, Br, or F atom, or a methyl, methoxy or ethoxy radical.

Conventionally, Aminopyrine, Mefenamic acid, Flufenamic acid and others were known as an anti-inflammatory and an analgesic, however, they possessed the disadvantage of causing gastroenteric trouble. We have found that these novel quinazolinedione derivatives have excellent anti-inflammatory action and analgesic action, as described later, without causing gastroenteric trouble.

Thus, one of the objects of the present invention is to provide the novel quinazolinedione derivatives having the excellent anti-inflammatory action and analgesic action.

Further, another object of the present invention is to provide the process for producing such novel quinazolinedione derivatives in high yield and advantageously.

According to the present invention, the aforesaid quinazolinedione derivatives are produced by reacting a compound of formula:



(II)

(wherein R_2 and/or R_3 represent the same as mentioned above) with an alkylating or acylating agent containing the group R_1, as defined above, e.g. a compound of formula R_1X (wherein R_1 is as defined above and X represents a halogen atom, or with a compound of formula $(R)_2SO_4$ wherein R represents a methyl or ethyl group, as alkylating agent. Consequently, the reaction of the present invention can be understood as being alkylation or acylation.

[P

The abovementioned compounds used as starting reaction materials in the present invention can be obtained in good yield by reacting N-phenylanthranilic acid or N-substituted phenylanthranilic acid with urea.

The quinazolinedione derivatives used as the aforesaid starting reaction materials include 1 - phenyl - 2,4(1H, 3H) - quinazolinedione or 1 - substituted phenyl - 2,4(1H, 3H) - quinazolinedione, for example, 1 - (3' - trifluoromethylphenyl - 2,4(1H, 3H) - quinazolinedione, 1 - (3' - chlorophenyl) - 2,4-(1H, 3H) - quinazolinedione, 1 - (2',3' - dichlorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (2' - chlorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (4' - chlorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (3',4' - dichlorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (2',6' - dichlorophenyl) - 2,4-(1H, 3H) - quinazolinedione, 1 - (3' - fluorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (4' - fluorophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (3' - bromophenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (2',3' - dimethylphenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (3' - methoxyphenyl) - 2,4(1H, 3H) - quinazolinedione, 1 - (4' - ethoxyphenyl) - 2,4-(1H, 3H) - quinazolinedione and 1 - (3' - methylphenyl) - 2,4(1H, 3H) - quinazolinedione.

In the group of compounds used as alkylating or acylating agent of the abovementioned starting reaction materials in the present invention expressed by the general formula R_1X, R_1 can for example, either be saturated or unsaturated alkyl or alkyl radical substituted by aryl-, halogen-, hydroxy-, amino-, alkoxy-, alkylthio-, phenoxy-, acyloxy-, acyl-, carbamoyloxy- or carbamoylalkoxy-radical, and said compounds include, for example, ethyl iodide, n-butyl bromide, iso-amyl iodide, benzyl bromide, 1-bromo-2-chloroethane, 2-diethylaminoethyl chloride, ethylene bromohydrin, chloromethyl ethyl ether, 2-bromoethyl acetate, 1-chloro-2-(N,N-dimethylcarbamoyloxy)-ethane, *p*-chlorobenzoyl chloride, acetyl chloride, benzoyl chloride, propionyl chloride, dimethylamino-propyl chloride, 2-bromoethyl ethyl ether and 2-bromoethyl benzoate. Further, the other group of compounds used as alkylating agent same as above is expressed by the general formula $(R)_2SO_4$, wherein R can be methyl or ethyl radical, dimethyl sulfate being more typical.

The reaction in the present invention is preferred to be performed in the presence of metallic compounds such as a sodium alcoholate, sodamide and sodium hydride, organic base such as pyridine and trialkylamine, or inorganic base such as alkali hydroxide and alkali carbonate.

Further, since the reaction of the present invention is usually made in an organic solvent such as acetone or dimethylformamide, it is carried out at a wide range of temperature. Consequently, the reaction temperature is not critical but can be either normal, warm or cool.

The compounds obtained according to the present invention show significant anti-inflammatory action and analgesic action as is apparent from the experimental tests as set forth below.

According to a further feature of the present invention, there are provided pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I, as defined above, in association with at least one pharmaceutically acceptable vehicle, diluent, excipient, or carrier.

Tests have been performed on acute toxicity, anti-inflammatory effect and analgesic effect of the invented compounds.

Testing Method of Acute Toxicity

Tragacanth emulsion was given intraperitoneally to healthy dd mice of 15 to 20g, and LD_{50} and its 95% confidence limits were calculated by Litchfield-Wilcoxon method from the lethal number after 72 hours.

Testing Method of Anti-inflammatory Effect

The drugs subjected to this test were given intragastrically to healthy female Wistar rats of 100 to 140 g, the inflammatory substance, carrageenin (1%, 0.1 ml), was injected subcutaneously into the soles of the rats' hind legs after 60 minutes, and the inhibition rates (%) against edema were measured by comparing the edema consequently arisen to the tested rats with the controls to which the drugs were not given. The amount of drugs given was 200 mg/kg and the mean inhibition rates were shown of 4 to 5 rats in a group.

In performing the above test, not only the compounds obtained by the present invention were employed, but the conventionally known compounds such as Mefenamic acid and Flufenamic acid were also subjected to the same test. The comparisons between the former and the latter were shown in the following table.

	Compounds	Acute Toxicity LD_{50} mg/kg i.p. 95% C.L.	Anti-inflammatory Effect Inhibition Rates Against Edema Induced by Carrageenin
Test Examples of the Compounds Obtained by the Present Invention	1-(3'-trifluoromethylphenyl)-3-methyl-2,4(1H, 3H)-quinazolinedione	360 (340—381)	+++
	1-(3'-trifluoromethylphenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione	373 (341)—408)	++++
	1-(3'-trifluoromethyl)-3-(2''-chloroethyl)-2,4(1H, 3H)-quinazolinedione	>800	+++
	1-(3'-trifluoromethylphenyl)-3-(2''-diethylaminoethyl)-2,4(1H, 3H)-quinazolinedione hydrochloride	158 (137—182)	++++
	1-(3'-trifluoromethylphenyl)-3-(2''-hydroxyethyl)-2,4-(1H, 3H)-quinazolinedione	253 (220—291)	++++
	1-(3'-trifluoromethylphenyl)-3-(2''-ethoxyethyl)-2,4-(1H, 3H)-quinazolinedione	460 (430—492)	++++
	1-(3'-trifluoromethylphenyl)-3-(2''-acetoxyethyl)-2,4-(1H, 3H)-quinazolinedione	>400	+++
	1-(3'-chlorophenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione	>800	++++
	1-(3'-chlorophenyl)-3-(2''-hydroxyethyl)-2,4(1H, 3H)-quinazolinedione	>400	++++
	1,3'-fluorophenyl)-3-ethyl-2,4-(1H, 3H)-quinazolinedione	>400	++++
Comparison	Mefenamic acid	420 (395—458)	+++
	Flufenamic acid	200 (180—222)	+++

In the above table +++ shows that the mean inhibition rate is 30 — 39%, and ++++ shows that said rate is more than 40%.

Testing Method of Analgesic Effect
Morphinized Haffner Method

The test was performed by employing healthy male dd-mice of 15—17 g, a single group consisted of 10 mice, with regard to inhibition of "withdrawal" against pressing at the root of the tail using in combination with the threshold dose (2.5 mg/kg s.c.) of Morphine hydrochloride. The test drugs had been given intragastrically 30 minutes before morphine was given, and ED_{50} and 95% confidence limits were calculated by Litchfield-Wilcoxon method from its result.

Acetic Acid Stretching Method

This test was performed by employing

healthy male dd mice of 15—17 g, a single group consisted of 6 to 8 mice, with regard to inhibition of stretching (or squirm) symptoms induced by intraperitoneal injection 0.1 ml/10 g of 0.6% acetic acid. The test drugs had been given intragastrically 30 minutes before acetic acid was given, and ED_{50} and 95% confidence limits were calculated by Litchfield-Wilcoxon method from its result.

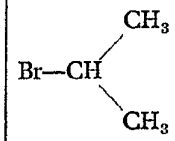
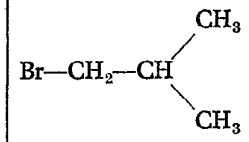
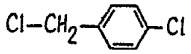
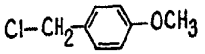
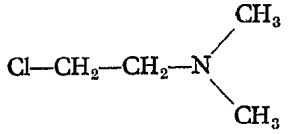
In performing the above test, not only the compounds obtained by the present invention were employed, but the conventionally known compounds such as Mefenamic acid, Flufenamic acid and Aminopyrine were also subjected to the same test.

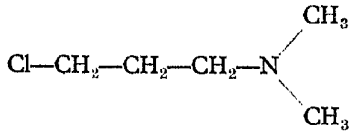
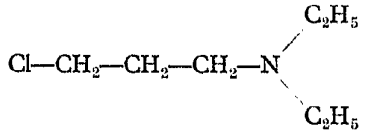
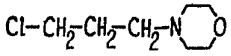
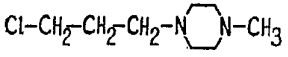
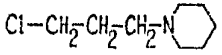
The comparison between the former and the latter is shown in the following table.

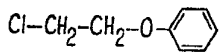
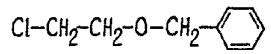
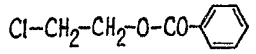
	Compounds	Testing Method: Acetic Acid Stretching method ED_{50}=mg/kg P.O. (C.L. 95%)	Testing Method: Morphinized Haffner method ED_{50}=mg/kg P.O. (C.L. 95%)
Test Examples of the Compounds Obtained by the Present Invention	1-(3'-trifluoromethylphenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione	100>33% Peak	148 (135—163)
	1-(3'-trifluoromethylphenyl)-3-(2''-hydroxyethyl)-2,4-(1H, 3H)-quinazolinedione	35 (28—43)	38 (26—54)
	1-(3'-trifluoromethylphenyl)-3-(2''-ethoxyethyl)-2,4(1H, 3H)-quinazolinedione	200>60% Peak	100>60% Peak
	1-(3'-trifluoromethylphenyl)-3-(2''-acetoxyethyl)-2,4-(1H, 3H)-quinazolinedione	94 (70—126)	124 (114—135)
	1-(3'-chlorophenyl)-3-ethyl-2,4(1H, 3H)-quinazolinedione	167 (140—223)	100>60% Peak
	1-(3'-chlorophenyl)-3-(2''-hydroxyethyl)-2,4(1H, 3H)-quinazolinedione	56 (44—72)	75>55% Peak
	1-(3'-chlorophenyl)-3-(2''-ethoxyethyl)-2,4(1H, 3H)-quinazolinedione	82 (50—134)	130>50% Peak
	1-(3'-chlorophenyl)-3-(2''-acetoxyethyl)-2,4(1H, 3H)-quinazolinedione	65 (45—94)	75>60% Peak
Comparison	Aminopyrine	93 (60—143)	65 (45—94)
	Mefenamic Acid	134 (100—180)	140 (114—172)
	Flufenamic Acid	170 (121—238)	200>35% Peak

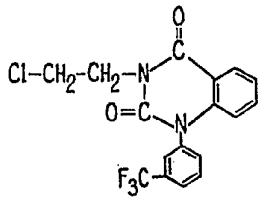
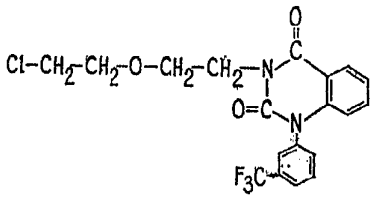
The following examples are given for illustrating the invention.

Examples of quinazolinedione derivatives produced according to the present invention:—

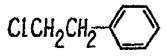
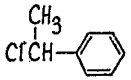
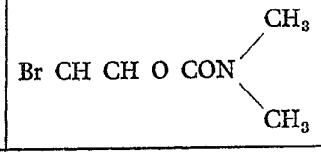
	*I R X	product			
		molecular formula	m.p. or b.p. (°C).	recrystallization solvent	appearance
1	$Br—CH_2—CH_2—CH_3$	$C_{18}H_{15}F_3N_2O_2$	m.p. 153	methanol	colorless prisms
2		$C_{18}H_{15}F_3N_2O_2$	m.p. 131—3	,,	,,
3		$C_{19}H_{17}F_3N_2O_2$	m.p. 111—3	,,	,,
4	$Br—CH_2—CH_2—CH_2—CH_2—CH_3$	$C_{20}H_{19}F_3N_2O_2$	m.p. 102—3	,,	,,
5	$Br—CH_2—CH_2—CH_2—CH_2—CH_2—CH_3$	$C_{21}H_{21}F_3N_2O_2$	m.p. 77—8	,,	,,
6	$Br—CH_2—CH=CH_2$	$C_{18}H_{13}F_3N_2O_2$	m.p. 123—4	,,	,,
7		$C_{22}H_{14}ClF_3N_2O_2$	m.p. 196—7	ethanol	,,
8		$C_{23}H_{17}F_3N_2O_3$	m.p. 203—4	,,	,,
9	$Br—CH_2—CH_2—CH_2—Cl$	$C_{18}H_{14}ClF_3N_2O_2$	m.p. 134—5	methanol	,,
10		$C_{19}H_{19}ClF_3N_3O_2$	m.p. 137—8 (hydrochloride)	ethanol + n-hexane	,,

	*I R X	product			
		molecular formula	m.p. or b.p. (°C).	recrystallization solvent	appearance
11		$C_{19}H_{21}ClF_3N_3O_2$	m.p. 245 (hydrochloride)	ethyl acetate	colorless prisme
12		$C_{22}H_{25}ClF_3N_3O_2$	m.p. 225—6 (hydrochloride)	"	"
13		$C_{22}H_{23}ClF_3N_3O_2$	m.p. 180—1 (hydrochloride)	"	"
14		$C_{23}H_{27}ClF_3N_4O_2$	m.p. 272—3 (dihydrochloride)	ethanol	
15		$C_{23}H_{25}ClF_3N_3O_2$	m.p. 252—3 (hydrochloride)	chloroform + n-hexane	pale yellow prisms
16	Cl—CH_2—CH_2—CH_2—OH	$C_{18}H_{15}F_3N_2O_3$	m.p. 106—7	methanol	colorless prisms
17	Cl—CH_2—CH(OH)—CH_2—OH	$C_{18}H_{15}F_3N_2O_4$	m.p. 154—5.5	ethanol	"

	*I R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
18	$Cl—CH_2—CH_2—O—CH_2—CH_3$	$C_{19}H_{17}F_3N_2O_3$	m.p. 11.7—8	methanol	colorless prisms
19	$Cl—CH_2—CH_2—O—CH_3$	$C_{13}H_{15}F_3N_2O_3$	b.p. 205	—	pale yellow oil
20		$C_{23}H_{17}F_3N_2O_3$	m.p. 155—6	methanol	colorless prisms
21		$C_{24}H_{19}F_3N_2O_3$	b.p. 235	—	pale yellow oil
22	$Cl—CH_2—CH_2—O—CH=CH_2$	$C_{19}H_{15}F_3N_2O_3$	m.p. 127—5—8.5	methanol	colorless prisms
23	$Cl—CH_2—CH_2—O—COC_2H_5$	$C_{20}H_{17}F_3N_2O_4$	m.p. 104—5	„	„
24		$C_{24}H_{17}F_3N_2O_4$	m.p. 150—1	„	„
25	$Cl—CH_2—COCH_3$	$C_{18}H_{13}F_3N_2O_3$	m.p. 184—5	„	„

	*I R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
26		$C_{32}H_{20}F_6N_4O_4$	m.p. 132—2.5	dimethylformamide + water	colorless prisms
27		$C_{34}H_{24}F_6N_4O_5$	m.p. 222—3	methanol + ethyl acetate	"
28	Cl—CH_2—CH_2—S—CH_2—CH_3	$C_{19}H_{17}F_3N_2O_2S$	m.p. 90—1	methanol	"
29	Cl—CH_2CH_2—O—CH_2—$CONH_2$	$C_{19}H_{16}F_3N_3O_4$	m.p. 153—4	"	"

The asterisk I shown in the above table represents the general formula of the compounds to be reacted with the above-mentioned 1-(3'-trifluoromethylphenyl)-2,4(1H,3H)-quinazolinedione in the process of the present invention.

	*II R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
30	$ClCOCH_2CH_3$	$C_{18}H_{13}F_3N_2O_3$	m.p. 177.5—8.5	methanol	colorless needles
31	$BrCH_2CH_2Br$	$C_{17}H_{12}BrF_3N_2O_2$	m.p. 144.5—5.5	"	colorless prisms
32		$C_{23}H_{17}F_3N_2O_2$	m.p. 122.5—3.5	"	colorless needles
33		$C_{23}H_{17}F_3N_2O_2$	m.p. 142.5—3.5	"	colorless prisms
34		$C_{20}H_{18}F_3N_3O_4$	m.p. 157—8	"	"

The asterisk II shown in the above table represents the general formula of the compounds to be reacted with the above-mentioned 1-(3'-trifluoromethylphenyl)-2,4(1H,3H)-quinazolinedione.

	*III	product			
	R X	molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
35	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{15}F\ N_2O_4$	m.p. 115.5—6.5	methanol	coloreless prisms
36	I CH_2CH_3	$C_{16}H_{13}FN_2O_2$	m.p. 147.5—8.5	"	"
37	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{17}FN_2O_3$	m.p. 109—10	"	"
38	$BrCH_2CH_2Cl$	$C_{16}H_{12}ClFN_2O_2$	m.p. 185.5—6.5	"	"

The asterisk III shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-fluorophenyl)-2,4(1H,3H)-quinazolinedione.

	*IV	product			
	R X	molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
39	I CH_2CH_3	$C_{16}H_{13}BrN_2O_2$	m.p. 187.5—8.5	ethanol	colorless prisms
40	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{17}BrN_2O_3$	m.p. 155—7	methanol	"
41	$BrCH_2CH_2OH$	$C_{16}H_{13}BrN_2O_3$	m.p. 161.5—2.0	methanol + water	"
42	$BrCH_2CH_2Cl$	$C_{16}H_{12}ClBrN_2O_2$	m.p. 184—6	dimethylformamide	pale yellow prisms

The asterisk IV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-bromophenyl)-2,4(1H,3H)-quinazolinedione.

	* V R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
43	$BrCH_2CH_2OCOCH_3$	$C_{20}H_{20}N_2O_4$	m.p. 181—3	methanol + dimethylformamide	pale yellow prisms
44	$BrCH_2CH_2OCH_2CH_3$	$C_{20}H_{22}N_2O_3$	m.p. 104—6	methanol	colorless needles

The asterisk V shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2',3'-dimethylphenyl)-2,4(1H,3H)-quinazolinedione.

	*VI R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
45	ICH_2CH_3	$C_{16}H_{13}FN_2O_2$	m.p. 213—5	methanol + dimethylformamide	colorless prisms
46	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{15}FN_2O_4$	m.p. 144—6	methanol	"
47	$BrCH_2CH_2Cl$	$C_{16}H_{12}ClFN_2O_2$	m.p. 205—8	dimethylformamide	"

The asterisk VI shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-fluorophenyl)-2,4(1H,3H)-quinazolinedione.

	* VII R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
48	ICH_2CH_3	$C_{17}H_{16}N_2O_2$	m.p. 139.5—40.5	methanol	colorless prisms
49	$BrCH_2CH_2OCOCH_3$	$C_{19}H_{18}N_2O_4$	m.p. 150—1	methanol + dimethylformamide	"
50	$BrCH_2CH_2OCH_2CH_3$	$C_{19}H_{20}N_2O_3$	m.p. 136—7	methanol	"

The asterisk VII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-methylphenyl)-2,4(1H,3H)-quinazolinedione.

	* VIII R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
51	ICH_2CH_3	$C_{17}H_{16}N_2O_3$	m.p. 164—5	methanol	colorless prisms

The asterisk VIII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3'-methoxyphenyl)-2,4(1H,3H)-quinazolinedione.

	* IX R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
52	ICH_2CH_3	$C_{18}H_{18}N_2O_3$	m.p. 191—3	ethanol + dimethylformamide	colorless prisms
53	$BrCH_2CH_2OCOCH_3$	$C_{20}H_{20}N_2O_5$	m.p. 134.5—5.5	methanol	"
54	$BrCH_2CH_2OCH_3CH_3$	$C_{20}H_{22}N_2O_4$	m.p. 136—8	"	"
55	$BrCH_2CH_2OH$	$C_{18}H_{18}N_2O_4$	m.p. 166.5—8.0	"	"

The asterisk IX shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-methoxyphenyl)-2,4(1H,3H)-quinazolinedione.

	* X R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
56	ICH_2CH_3	$C_{16}H_{13}ClN_2O_2$	m.p. 160—3	methanol	colorless prisms
57	$ICH_2CH_2CH_2CH_3$	$C_{18}H_{17}ClN_2O_2$	m.p. 144—5	"	colorless needles
58	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{15}ClN_2O_4$	m.p. 145—7	ethanol	pale yellow prisms
59	$BrCH_2CH_2Cl$	$C_{16}H_{12}ClN_2O_2$	m.p. 169—70	"	colorless prisms
60	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{17}ClN_2O_3$	m.p. 134—6	methanol	"
61	$ClCH_2COOCH_2CH_3$	$C_{18}H_{15}ClN_2O_4$	m.p. 181—3	ethanol	colorless needles
62	$BrCH_2CH_2OH$	$C_{16}H_{13}ClN_2O_2$	m.p. 145—6	methanol	"

The asterisk X shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(4'-chlorophenyl)-2,4(1H,3H)-quinazolinedione.

	* XI R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
63	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{15}ClN_2O_4$	m.p. 144—5	methanol	colorless prisms
64	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{17}ClN_2O_3$	m.p. 129—30	"	colorless needles
65	$BrCH_2CH_2OH$	$C_{16}H_{13}ClN_2O_3$	m.p. 149—52	"	colorless prisms

The asterisk XI shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2'-chlorophenyl)-2,4(1H,3H)-quinazolinedione.

	* XII R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
66	ICH_2CH_3	$C_{16}H_{13}ClN_2O_2$	m.p. 179—80	ethanol	colorless prisms
67	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{17}ClN_2O_3$	m.p. 115—6	"	"
68	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{15}ClN_2O_4$	m.p. 136—7	methanol	"
69	$BrCH_2CH_2OH$	$C_{15}H_{13}ClN_2O_3$	m.p. 149.0—50.5	"	"
70	$BrCH_2CH_2CH_2OH$	$C_{17}H_{15}ClN_2O_3$	m.p. 136.5—9.5	"	"
71	$ClCH_2COOCH_2CH_3$	$C_{18}H_{15}ClN_2O_4$	m.p. 127—9	"	"
72	$BrCH_2CH_2Cl$	$C_{16}H_{12}Cl_2N_2O_2$	m.p. 170—1	"	"
73	$ICH_2CH_2CH_2CH_3$	$C_{18}H_{17}ClN_2O_2$	m.p. 141—6	"	"
74	$BrCH_2CH(CH_3)_2$	$C_{18}H_{17}ClN_2O_2$	m.p. 121—3	"	"
75	$ClCH_2CH_2CH_3$	$C_{17}H_{15}ClN_2O_2$	m.p. 132—4	"	"
76	$ICH(CH_3)_2$	$C_{17}H_{15}ClN_2O_2$	m.p. 140.0—1.5	"	colorless needles

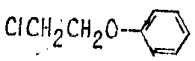
The asterisk XII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentionted 1-(3'-chlorophenyl)-2,4(1H,3H)-quinazolinedione.

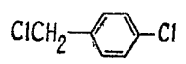
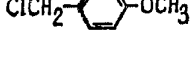
	* XIII R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
77	ICH_2CH_3	$C_{16}H_{12}Cl_2N_2O_2$	m.p. 166.0—7.5	methanol	colorless prisms
78	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{16}Cl_2N_2O_3$	m.p. 102.5—4.0	"	"
79	$BrCH_2CH_2OH$	$C_{16}H_{12}Cl_2N_2O_3$	m.p. 144.5—6.0	methanol + water	colorless needles

The asterisk XIII shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(2',3'-dichlorophenyl)-2,4(1H,3H)-quinazolinedione.

	* XIV R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
80	ICH_2CH_3	$C_{16}H_{12}Cl_2N_2O_2$	m.p. 139—41	methanol	colorless prisms
81	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{14}Cl_2N_2O_4$	m.p. 120—1	"	colorless needles
82	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{16}Cl_2N_2O_3$	m.p. 114.0—5.5	"	"
83	$BrCH_2CH_2OH$	$C_{16}H_{12}Cl_2N_2O_3$	m.p. 145—7	"	pale yellow prisms
84	$BrCH_2CH_2Cl$	$C_{16}H_{11}Cl_3N_2O_2$	m.p. 155—6	ethanol + dimethylformamide	colorless prisms

The asterisk XIV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-(3',4'-dichlorophenyl)-2,4(1H,3H)-quinazolinedione.

	* XV	product			
	R X	molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
85	ICH_2CH_3	$C_{16}H_{14}N_2O_2$	m.p. 196.5—7.5	ethanol	colorless prisms
86	$ICH_2CH_2CH_2CH_3$	$C_{18}H_{18}N_2O_2$	m.p. 106—7	methanol + water	„
87	$ClCH_2COOCH_2CH_3$	$C_{18}H_{16}N_2O_4$	m.p. 164—5	methanol	„
88	$BrCH_2CH_2OH$	$C_{16}H_{14}N_2O_3$	m.p. 205.5—8.0	„	„
89	$BrCH_2CH_2OCH_2CH_3$	$C_{18}H_{18}N_2O_3$	m.p. 93—5	„	„
90	$BrCH_2CH_2OCOCH_3$	$C_{18}H_{16}N_2O_4$	m.p. 159—60.5	„	„
91	$BrCH_2CH_2Cl$	$C_{16}H_{13}ClN_2O_2$	m.p. 214.0—6.5	dimethylformamide	„
92	$BrCH_2CH_2CH_2Cl$	$C_{17}H_{15}ClN_2O_2$	m.p. 153—4	methanol	pale yellow prisms
93	$ClCH(CH_3)COOCH_2CH_2$	$C_{19}H_{18}N_2O_4$	m.p. 129—30	„	„
94	$BrCH_2OCH_2CONH_2$	$C_{18}H_{17}N_3O_4$	m.p. 159.5—60.5	„	yellow needles
95		$C_{22}H_{18}N_2O_3$	m.p. 188—9	dimethylformamide	colorless needles

	* XV R X	product			
		molecular formula	m.p. or b.p. (°C.)	recrystallization solvent	appearance
96		$C_{23}H_{15}ClN_4O_4$	m.p. 179—80	methanol	»
97		$C_{22}H_{18}N_2O_3$	m.p. 178—9	methanol + dimethylformamide	colorless prisms

The asterisk XV shown in the above table represents the general formula of the compounds to be reacted in the process of the present invention with the above-mentioned 1-phenyl-2,4(1H,3H)-quinazolinedione.

The following Examples illustrate the process of the present invention:

Example 98

The mixture of 5.4 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, 1.3 g dimethylsulfate, and 30 cc acetone was heated for 2 hours at 50—70°C on a water bath, then the solvent was distilled off. The residue was then poured into 20% sodium hydroxide solution under cooling for neutralization, the crystals produced were filtered, washed with water and dried, and, upon recrystallization from ethanol, 4.1 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - methyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	189—189.5°C
ultimate analysis value	$C_{16}H_{11}F_3N_2O_2$
theoretical values	C: 60.00 H: 3.46 N: 8.75
found values	C: 60.01 H: 3.66 N: 8.46

Example 99

To 5.4 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, and 40 cc dried dimethylformamide was added 1 g of 50% sodium hydride; the mixture was stirred for one hour. Then, 3.6 g ethyl iodide were further added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystalliza-

tion from ethanol, 5 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	156—157°C
ultimate analysis value	$C_{17}H_{13}F_3N_2O_2$
theoretical values	C: 61.07 H: 3.92 N: 8.38
found values	C: 61.07 H: 3.98 N: 8.32

Example 100

0.6 g metallic sodium was added to 10 cc 1-butanol and sodium 1-butoxide was formed. To this was added the solution obtained by dissolving 6.5 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione in 20 cc dried dimethylformamide, said solution mixture was stirred for 1 hour, then 10.5 g of n-butyl bromide were added and the mixture was stirred for 3 hours at room temperature. Water was further added, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6.1 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (n - butyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	126—127°C
ultimate analysis value	$C_{19}H_{17}F_3N_2O_2$
theoretical values	C: 62.98 H: 4.73 N: 7.73
found values	C: 63.39 H: 5.04 N: 7.95

Example 101

0.5 g sodamine was added to the mixture of 3.6 g 1 - (3′ - trifluoromethylphenyl) - 2,4 - (1H,3H) - quinazolinedione and 30 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5.9 g of isopentyl iodide were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 3.9 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (isopentyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	115—115.5°C
ultimate analysis value	$C_{20}H_{19}F_3N_2O_2$
theoretical values	C: 63.82 H: 5.09 N: 7.44
found values	C: 63.95 H: 5.18 N: 7.38

Example 102

1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4 g of benzyl bromide were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - benzyl - 2,4-(1H,3H) - quinazolinedione were obtained.

melting point	183—184°C
ultimate analysis value	$C_{23}H_{15}F_3N_2O_2$
theoretical values	C: 66.66 H: 3.81 N: 7.07
found values	C: 66.67 H: 3.90 N: 6.79

Example 103

1.3 g of 50% sodium hydride was added to the mixture of 7 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then 4.3 g 1-bromo-2-chloroethane were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 6.3 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (2″ - chloroethyl) - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point	136—137°C
ultimate analysis value	$C_{17}H_{12}ClF_3N_2O_2$
theoretical values	C: 55.37 H: 3.28 N: 7.60
found values	C: 55.17 H: 3.39 N: 7.50

Example 104

1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4.5 g diethylaminoethyl chloride were added and the mixture was heated for 3 hours at 40—45°C. The solvent was then distilled under reduced pressure, the residue was added with water, and an oily substance was obtained. Said substance was extracted with ether and, after dehydration, 23% ethanol hydrochloric acid was added under cooling for acidification. Then, the solvent was distilled off under reduced pressure, the residue was recrystallized from ethanol and ethyl acetate, and 6.2 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (2″ - diethylaminoethyl) - 2,4(1H, 3H) - quinazolinedione hydrochloride were obtained.

melting point	229—230°C
ultimate analysis value	$C_{21}H_{23}ClF_3N_3O_2$
theoretical values	C: 57.08 H: 5.25 N: 9.51
found values	C: 57.05 H: 5.47 N: 9.43

Example 105

2.4 g of 50% sodium hydride were added to the mixture of 9.2 g 1 - (3′ - trifluoromethyl-

phenyl) - 2,4(1H, 3H) - quinazolinedione and 80 cc dried dimethylformamide, and the mixture was stirred for one hour. Then, ethylene bromohydrin was added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 10 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (2″ - hydroxyethyl) - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point	138—139°C
ultimate analysis value	$C_{17}H_{13}F_3N_2O_3$
theoretical values	C: 58.29 H: 3.74 N: 8.00
found values	C: 58.40 H: 3.71 N: 8.11

Example 106

1 g of 50% sodium hydride was added to the mixture of 5.4 g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione and 40 cc dried dimethylformamide, and the mixture was stirred for one hour. Then 3.4 g of chloromethyl ethyl ether were added and the mixture was reacted for 3 hours. The solvent was then distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 5 g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - ethoxymethyl - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point	157.5—159°C
ultimate analysis value	$C_{18}H_{15}F_3N_2O_3$
theoretical values	C: 59.34 H: 4.15 N: 7.69
found values	C: 59.61 H: 4.42 N: 7.58

Example 107

1 g of 50% sodium hydride was added to the mixture of 5.4g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 6.7g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 5.7g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (2″-acetoxyethyl) - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point	111.5—112°C
ultimate analysis value	$C_{19}H_{15}F_3N_2O_4$
theoretical values	C: 58.16 H: 3.85 N: 7.14
found values	C: 58.28 H: 3.64 N: 7.15

Example 108

0.5g of 50% sodium hydrate was added to the mixture of 2.7g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione and 20cc dried dimethylformamide, and the mixture was stirred for one hour. Then, a solution obtained by dissolving 3.4g 1 - (3′ - trifluoromethylphenyl) - 3 - monochloromethoxymethyl - 2,4(1H,3H) - quinazolinedione in 20cc dried dimethylformamide was added and the mixture was reacted for 4 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol and ethyl acetate, 58g of colorless prisms of bis - [3 - (1 - 3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione]-methyl ether were obtained.

melting point	114—114.5°C
ultimate analysis value	$C_{32}H_{20}F_6N_4O_5$
theoretical values	C: 58.72 H: 3.08 N: 8.56
found values	C: 58.90 H: 2.86 N: 8.57

Example 109

1g of 50% sodium hydride was added to the mixture of 5.4g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4.3g of 1 - chloro - 2 - (N, N - dimethylcarbamoyloxy)-ethane were added and the mixture was reacted for 4 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water and the residue was held under cooling. The crystals produced were recrystallized from methyl alcohol, and 5.2g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - (2″-N, N - dimethylcarbamoyloxyethyl) - 2,4(1H, 3H)-quinazolinedione were obtained.

melting point	157—158°C
ultimate analysis value	$C_{20}H_{18}F_3N_3O_4$
theoretical values	C: 57.01 H: 4.31 N: 9.97
found values	C: 57.23 H: 4.20 N: 10.0

Example 110

1g of sodium hydride was added to the mixture of 5.4g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H, 3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 4g of *p*-chlorobenzoyl chloride were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from ethanol, 5.7g of colorless prisms of 1-(3′-trifluoromethylphenyl) - 3 - (4″ - chloro-

benzoyl) - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point	196—197°C
ultimate analysis value	$C_{22}H_{12}ClF_3N_2O_3$
theoretical values	C: 61.33 H: 3.28 N: 6.50
found values	C: 61.45 H: 3.32 N: 6.33

Example 111

0.7g of sodium hydride was added to the mixture of 3.1g 1 - (3′ - trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 2g of acetyl chloride were added dropwise and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered and dried, and, upon recrystallization from methanol, 2.5g of colorless prisms of 1 - (3′ - trifluoromethylphenyl) - 3 - acetyl-2,4(1H,3H) - quinazolinedione were obtained.

melting point	165—166°C
ultimate analysis value	$C_{17}H_{11}F_3N_2O_3$
theoretical values	C: 58.62 H: 3.18 N: 8.05
found values	C: 58.87 H: 3.26 N: 7.91

Example 112

The mixed solution consisting of 2g 1-(3′-trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, 30cc dried dimethylformamide and 1.6g dried pyridine was heated to 80°C. Then, 4.2g of benzoyl chloride were added dropwise and the mixture was reacted for 3 hours at 80—90°C. It was then filtered, the filtrate was distilled under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3′ - trifluoromethylphenyl)-3 - benzoyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	166—167°C
ultimate analysis value	$C_{22}H_{13}F_3N_2O_3$
theoretical values	C: 64.39 H: 3.19 N: 6.83
found values	C: 64.24 H: 3.30 N: 6.87

Example 113

A mixed solution consisting of 3g 1-(3′-trifluoromethylphenyl) - 2,4(1H,3H) - quinazolinedione, 30cc dimethylformamide and 4g triethylamine was heated to 80°C. Then, 2.8g of propionyl chloride were added dropwise and the mixture was reacted for 3 hours at 80—90°C. It was then filtered, the filtrate was dried by evaporation under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 2.8g of colorless needles of 1 - (3′ - trifluoromethylphenyl)-3 - propionyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	177.5—178.5°C
ultimate analysis value	$C_{15}H_{11}F_3N_2O_4$
theoretical values	C: 56.02 H: 3.96 N: 10.32
found values	C: 56.21 H: 3.83 N: 10.24

Example 114

The mixture of 5g 1 - (3′ - chlorophenyl)-2,4(1H, 3H) - quinazolinedione, 1.3g dimethyl sulfate and 50cc acetone was heated for 2 hours at 50—70°C on a water bath, then the solvent was distilled off, the residue was poured into 20% sodium hydroxide solution under cooling for neutralization, the crystals produced were filtered, washed with water and dried, and, upon recrystallization from dimethylformamide, 4.2g of colorless prisms of 1 - (3′ - chlorophenyl) - 3 - methyl - 2,4-(1H, 3H) - quinazolinedione were obtained.

melting point	223—226°C
ultimate analysis value	$C_{15}H_{11}ClN_2O_2$
theoretical values	C: 62.84 H: 3.87 N: 9.77
found values	C: 62.75 H: 3.84 N: 9.79

Example 115

1g of 50% sodium hydride was added to the mixture of 4.1g 1 - (3′ - chlorophenyl)-2,4(1H, 3H) - quinazolindone and 40cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.3g of glycerol-α-monochlorohydrin were added and the mixture was reacted for 1.5 hours at room temperature. The solvent was distilled off under reduced pressure, the residue was added with water, the crystals produced were filtered, and, upon recrystallization from methyl alcohol, 4.2g of colorless needles of 1 - (3′ - chlorophenyl) - 3 - (2″, 3″ - dihydroxypropyl)-2,4(1H, 3H) - quinazolinedione were obtained.

melting point	163—164°C
ultimate analysis value	$C_{17}H_{15}ClN_2O_4$
theoretical values	C: 58.88 H: 4.36 N: 8.08
found values	C: 59.08 H: 4.37 N: 8.07

Example 116

0.5g of 50% sodium hydride was added to the mixture of 1.5g 1 - (2′, 3′ - dichlorophenyl) - 2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were then recrystallized from ethanol, and 1.7g of colorless needles of 1 - (2′, 3′ - dichlorophenyl) - 3-

(2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point ultimate	183.5—184.5°C
analysis value	$C_{18}H_{14}Cl_2N_2O_4$
theoretical values	C: 54.98 H: 3.59 N: 7.13
found values	C: 55.00 H: 3.53 N: 7.14

Example 117

0.6g metallic sodium was added to 10cc ethyl alcohol, and sodium ethoxide was formed. Then, a solution obtained by dissolving 5.8g of 1 - (2' - chlorophenyl) - 2,4-(1H,3H) - quinazolinedione in 20ml dried dimethylformamide was added. Further, 6.6g of ethyl iodide were added and reaction was allowed to take place for 3 hours at room temperature. Then, water was added, the crystals produced were filtered and dried, and, upon recrystallization from methyl alcohol, 5.4g of colorless prisms of 1 - (2' - chlorophenyl) - 3 - ethyl - 2,4(1H, 3H) - quinazolinedione were obtained.

melting point ultimate	145—146°C
analysis value	$C_{16}H_{13}ClN_2O_2$
theoretical values	C: 63.90 H: 4.36 N: 9.31
found values	C: 63.96 H: 4.27 N: 9.42

Example 118

0.7g of 50% sodium hydride was added to the mixture of 2.7g 1 - (4' - chlorophenyl)-2,4(1H, 3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.6g of 3-dimethylamino - propyl chloride were added and the mixture was reacted for 3 hours at room temperature. The solvent was distilled under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methyl alcohol, 2.9g of colorless needles of 1 - (4' - chlorophenyl) - 3 - (3'' - dimethylaminopropyl)-2,4(1H, 3H) - quinazolinedione were obtained.

melting point ultimate	164.5—165.5°C
analysis value	$C_{19}H_{20}ClN_3O_2$
theoretical values	C: 63.77 H: 5.63 N: 11.74
found values	C: 63.62 H: 5.65 N: 11.50

Example 119

1.1g sodamide were added to the mixture of 4.5g 1 - (3', 4' - dichlorophenyl) - 2,4(1H, 3H) - quinazolinedione and 40 ml dimethylformamide, and the mixture was stirred for one hour. Then 7.3g of ethyl bromoacetate were added and the mixture was reacted for one hour. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from the mixed solvent consisting of dimethylformamide and ethanol, 4.6g of colorless prisms of ethyl 1 - (3', 4' - dichlorophenyl) - 2,4-(1H,3H) - quinazolinedione 3-acetate were obtained.

melting point ultimate	157.5—158.5°C.
analysis value	$C_{18}H_{14}Cl_2N_2O_4$
theoretical values	C: 54.98 H: 3.59 N: 7.12
found values	C: 54.93 H: 3.53 N: 7.06

Example 120

0.6g of 50% sodium hydride was added to the mixture of 1.7g 1 - (2', 6' - dichlorophenyl)) - 2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was reacted for one hour at room tempera. Then, 5g of ethyl iodide were added, and the mixture was further reacted for two hours at room temperature. Then, the solvent was distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.5 g of colorless prisms of 1 - (2', 6' - dichlorophenyl) - 3 - ethyl - 2,4-(1H,3H) - quinazolinedione were obtained.

melting point ultimate	174.5—175.5°C
analysis value	$C_{16}H_{12}Cl_2N_2O_2$
theoretical values	C: 57.33 H: 3.61 N: 8.36
found values	C: 57.43 H: 3.49 N: 8.43

Example 121

0.8g of 50% sodium hydride was added to the mixture of 3g 1 - (3' - fluorophenyl)-2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.7g of ethylene bromohydrin were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were then recrystallized from the mixed solvent consisting of methanol, and water, and 2.9g of colorless prisms of 1 - (3' - fluorophenyl) - 3 - (2'' - hydroxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point ultimate	136.5—137.5°C
analysis value	$C_{16}H_{13}F N_2O_3$
theoretical values	C: 63.99 H: 4.46 N: 9.33
found values	C: 64.15 H: 4.07 N: 9.37

Example 122

The mixture of 1.8g 1 - (4' - fluorophenyl)-2,4(1H,3H) - quinazolinedione, 3g diethyl sulfate and 50cc acetone was heated for 2 hours at 50—70°C on a waterbath. The solvent was then distilled off, the residue was poured into 20% sodium hydroxide solution under cooling for neutralization, the crystals produced were filtered and washed with water,

and, upon recrystallization from the mixed solvent consisting of methanol and dimethylformamide, 1.6g of colorless prisms of 1-(4'-fluorophenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolidione were obtained.

melting point	213—215°C
ultimate analysis value	$C_{16}H_{13}FN_2O_2$
theoretical values	C: 67.60 H: 4.61 N: 9.85
found values	C: 67.51 H: 4.38 N: 9.91

Example 123

0.7g of 50% sodium hydride was added to the mixture of 1.8g 1 - (4' - fluorophenyl)-2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3.2g of 2-bromoethyl ethyl ether were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from the mixed solvent consisting of methanol and water, 1.8g of colorless needles of 1 - (4' - fluorophenyl) - 3-(2'' - ethoxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	112—113°C
ultimate analysis value	$C_{18}H_{17}FN_2O_3$
theoretical values	C: 65.85 H: 5.22 N: 8.53
found values	C: 65.79 H: 5.34 N: 8.64

Example 124

0.4g of 50% sodium hydride was added to the mixture of 2g 1 - (3' - bromophenyl)-2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethyl acetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3' - bromophenyl) - 3-(2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	145—146°C
ultimate analysis value	$C_{18}H_{15}BrN_2O_4$
theoretical values	C: 53.61 H: 3.75 H: 6.95
found values	C: 53.46 H: 3.71 N: 6.80

Example 125

0.6g metallic sodium was added to 10ml ethanol and sodium ethoxide was formed. Then, a solution obtained by dissolving 5.3g 1 - (2',3' - dimethylphenyl) - 2,4(1H,3H) quinazolinedione in 20cc dried dimethylformamide was added. Further, 4.6g of ethyl iodide were added, and the mixture was reacted for 3 hours at room temperature. Then, water was added, the crystals produced were filtered, and, upon recrystallization from methanol, 4.7g of colorless needles of 1 - (2',3' - dimethylphenyl) - 3 - ethyl - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	202—205°C
ultimate analysis value	$C_{18}H_{18}N_2O_2$
theoretical values	C: 73.45 H: 6.16 N: 9.52
found values	C: 72.80 H: 5.93 N: 9.64

Example 126

0.5g of 50% sodium hydride was added to the mixture of 1.5g 1 - (3' - methoxyphenyl)-2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 5g of 2-bromoethylacetate were added and the mixture was reacted for 3 hours at room temperature. The solvent was distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.8g of colorless prisms of 1 - (3' - methoxyphenyl) - 3-(2'' - acetoxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	130—131°C
ultimate analysis value	$C_{19}H_{18}N_2O_5$
theoretical values	C: 64.40 H: 5.12 N: 7.91
found values	C: 64.52 H: 4.96 N: 7.85

Example 127

0.2g of sodamide was added to the mixture of 1g 1 - (4' - ethoxyphenyl) - 2,4(1H,3H)-quinazolinedione and 20cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 1.9g of 1 - bromo - 2 - chloroethane were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 1.0g of colorless needles of 1 - (4' - ethoxyphenyl) - 3-(2'' - chloroethyl) - 2,4(1H,3H) - quinazolinedione was obtained.

melting point	144—146°C
ultimate analysis value	$C_{18}H_{17}ClN_2O_3$
theoretical values	C: 62.70 H: 4.97 N: 8.12
found values	C: 62.66 H: 4.96 N: 8.25

Example 128

0.6g of 50% sodium hydride was added to the mixture of 2.4g 1 - phenyl - 2,4-(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 6.8g of 2-bromoethyl benzoate were added and the mixture was reacted for 3 hours at room temperature.

The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were then recrystallized from the mixed solvent consisting of dimethylformamide and methanol, and 3.9g of 1 - phenyl - 3 - (2'' - benzoyloxyethyl)-2,4(1H,3H) - quinazolinedione were obtained.

melting point	150.5—151°C.
ultimate analysis value	$C_{23}H_{18}N_2O_4$
theoretical values	C: 71.49 H: 4.70 N: 7.25
found values	C: 71.41 H: 4.79 N: 7.35

Example 129

2.8g of propionyl chloride were added dropwise to the mixed solution consisting of 5.6g 1 - phenyl - 2,4(1H,3H) - quinazolinedione, 30cc dried dimethylformamide and 4g triethylamine, and the mixture was reacted for 3 hours at 80—90°C. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from methanol, 2.3g of colorless needles of 1 - phenyl - 3 - propionyl - 2,4(1H,3H)-quinazolinedione were obtained

melting point	154—155°C
ultimate analysis value	$C_{17}H_{14}N_2O_3$
theoretical values	C: 69.37 H: 4.79 N: 9.52
found values	C: 69.21 H: 4.87 N: 9.31

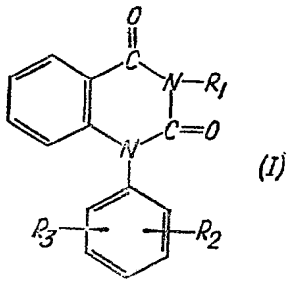
Example 130

0.7g of 50% sodium hydride was added to the mixture of 1.9g 1 - (3' - methylphenyl)-2,4(1H,3H) - quinazolinedione and 30cc dried dimethylformamide, and the mixture was stirred for one hour. Then, 3g of ethylene bromohydrin were added and the mixture was reacted for 3 hours at room temperature. The solvent was then distilled off under reduced pressure, to the residue was added water, the crystals produced were filtered, and, upon recrystallization from the mixed solvent consisting of methanol and water, 1.9g of colorless prisms of 1 - (3' - methylphenyl) - 3 - (2''-hydroxyethyl) - 2,4(1H,3H) - quinazolinedione were obtained.

melting point	152—154°C
ultimate analysis value	$C_{17}H_{16}N_2O_3$
theoretical values	C: 68.91 H: 5.44 N: 9.45
found values	C: 68.74 H: 5.24 N: 9.45

WHAT WE CLAIM IS:—

1. Compounds of formula:



(I)

wherein R_1 represents an alkyl, a substituted alkyl or an acyl radical; R_2 and R_3 each represent a hydrogen atom, a CF_3 group, a Cl, Br, or F atom, or a methyl, methoxy or ethoxy radical.

2. Compounds of formula I, as defined in Claim 1 wherein R_2 represents a trifluoromethyl group and R_3 represents a hydrogen atom.

3. Compounds of formula I, as defined in Claim 1 wherein R_2 represents a chlorine atom and R_3 represents a hydrogen atom.

4. Compounds of formula I, as defined in Claim 1, wherein R_2 and R_3 each represent a chlorine atom.

5. Compounds of formula I, as defined in Claim 1, wherein R_2 represents a fluorine atom and R_3 represents a hydrogen atom.

6. Compounds of formula I, as defined in Claim 1, wherein R_2 represents a bromine atom and R_3 represents a hydrogen atom.

7. Compounds of formula I, as defined in Claim 1, wherein R_2 and R_3 each represent a methyl group.

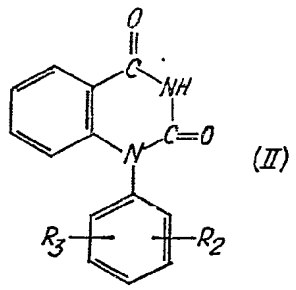
8. Compounds of formula I, as defined in Claim 1, wherein R_2 represents a methoxy group and R_3 represents a hydrogen atom.

9. Compounds of formula I, as defined in Claim 1, wherein R_2 represents an ethoxy group and R_3 represents a hydrogen atom.

10. Compounds of formula I, as defined in Claim 1, wherein R_2 and R_3 each represent a hydrogen atom.

11. Compounds of formula I, as defined in Claim 1, wherein R_2 represents a methyl group and R_3 represents a hydrogen atom.

12. A process for preparing compounds of formula I, as defined in Claim 1, which comprises reacting a compound of formula:



(II)

wherein R_2 and R_3 are as defined in Claim 1, with an alkylating or acylating agent containing the group R_1, as defined in Claim 1.

13. A process as claimed in Claim 12, wherein said alkylating or acylating agent is a compound having the general formula R_1X in which X represents a halogen atom.

14. A process as claimed in Claim 12, wherein said alkylating agent is a compound of formula $(R)_2SO_4$ in which R represents a methyl or ethyl group.

15. A process as claimed in any of Claims 12 to 14, wherein the reaction is effected in the presence of a sodium alcoholate, sodamide, sodium hydride; an organic base or an inorganic base.

16. A process as claimed in Claim 15, wherein the organic base comprises pyridine or a trialkylamine.

17. A process as claimed in Claim 15, wherein the inorganic base comprises at least one alkali metal hydroxide or alkali metal carbonate.

18. A process as claimed in any of Claims 12 to 17, wherein the reaction is effected in an organic solvent.

19. A process as claimed in Claim 18, wherein said organic solvent comprises acetone or dimethylformamide.

20. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I, as defined in Claim 1, in association with at least one pharmaceutically acceptable vehicle, diluent, excipient, or carrier.

21. Compounds of formula I, as defined in Claim 1, whenever prepared by a process as claimed in any of Claims 12 to 19.

22. A process for producing quinazolinedione derivatives substantially as herein described with reference to any one of the Examples given.

23. Compounds of formula I, as defined in Claim 1, substantially as herein described with reference to any of Examples 1 to 97.

24. Pharmaceutical compositions as claimed in Claim 20, substantially as herein described.

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